REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Mammals are generally thought to have five basic categories of taste perception: salt, sour, sweet, bitter, and *umami* (monosodium glutamate). The taste signals are sensed by specialized taste receptor cells (TRCs), which are organized into taste buds. Each taste bud comprises between about 50 and 100 individual cells grouped into a cluster that is between 20 and 40 microns in diameter. Nerve fibers enter from the base of the taste bud and synapse onto some of the taste receptor cells. Typically, a single TRC contacts several sensory nerve fibers, and each sensory fiber innervates several TRCs in the same taste bud.

TRCs of most, if not all, vertebrate species possess voltage-gated sodium, potassium, and calcium ion channels with properties similar to those of neurons. Different types of primary tastes appear to utilize different types of transduction mechanisms, and certain types of tastes may employ multiple mechanisms which may reflect varying nutritional requirements amongst species.

Bitter and sweet taste transduction are thought to involve cAMP and IP_3. The bitter compound denatonium causes calcium ion release from rat TRCs and the rapid elevation of IP_3 levels in rodent taste tissue. Since denatonium cannot pass the cell membrane, it has been suggested that it may activate G-protein-coupled receptors, whereby the α and/or $\beta\gamma$ G protein subunits would activate phospholipase C, leading to IP_3 generation and the release of calcium ions.

In recent years, a taste-specific G protein termed "gustducin," which is homologous to the retinal G protein, transducin, has been cloned and characterized. It is believed that gustducin plays a direct role in both bitter and sweet transduction. For example, gustducin and subunit (α - gustducin) null (knockout) mice had a reduced aversion to bitter compounds. Unexpectedly, the mice also exhibited a preference for sweet compounds suggesting involvement of gustducin in sweet transduction.

Recent biochemical experiments have demonstrated that taste receptor preparations activate transducin and gustducin in response to denatonium and other bitter compounds.

To thoroughly understand the molecular mechanisms underlying taste sensation, it is important to identify each molecular component in the taste signal transduction pathways. The present invention is directed to achieving this objective.

By the above amendments, claims 24–37 have been added. Support for these claims is found in the present application at, e.g., ¶ [0058] (claim 35), ¶ [0059] (claims 24–28), ¶¶ [0060] and [0063] (claims 29, 34), ¶¶ [0061]–[0062] (claims 30–32), ¶ [0063] (claim 33), and ¶ [0073] (claim 36).

The rejection of claim 17 under 35 U.S.C. § 112 (1st para.) for lack of written description is respectfully traversed. Not in acquiescence to the rejection, but solely to advance prosecution, applicants have amended claim 17 to recite a method for identifying a compound that induces the perception of a bitter taste by measuring the level of TRP8 activation in the presence of a test compound and comparing that level to a vehicle control (e.g., ¶¶ [0053]–[0058], particularly ¶ [0055]). See also claim 17 as originally filed. Since the present application fully describes the claimed method, the rejection of claim 17 under 35 U.S.C. § 112 (1st para.) should be withdrawn.

The rejection of claim 17 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed in view of the above amendments. Not in acquiescence to the rejection, but solely to advance prosecution, applicants have further amended claim 17 to recite isolated cells.

The rejection of claim 17 under 35 U.S.C. § 102(e) for anticipation by U.S. Patent Application Publication No. 2002/0164645 to Zucker et al. ("Zucker") is respectfully traversed in view of the above amendments.

Applicants maintain that the claims of the present application are entitled to benefit of the April 17, 2000, filing date of U.S. Provisional Patent Application No. 60/197,491 ("the Provisional Application"). Specifically, page 17, line 16 to page 19, line 16 of the Provisional Application discloses screening assays relating to TRP8, including a method for identifying a compound that induces the perception of a bitter taste. This method involves contacting a cell expressing the TRP8 channel protein with a test compound, measuring the level of TRP8 activation, and comparing the level of activation with a vehicle control (*see* page 18, lines 6–14 of the Provisional Application). Support for new claims 24–36 is found in the Provisional Application at the following passages: page 19, lines 12–16 (claim 35); page 19, line 17 to page 20, line 7 (claims 24–28); page 20, lines 8–18 (claims 29, 34); page 20, line 19 to page 21, line 23 (claims 30–32); page 21, lines 14–23 (claim 33); and

page 25, line 18 to page 26, line 3 (claim 36). Because the Provisional Application provides complete descriptive support for the claimed invention, the pending claims are entitled to benefit of an April 17, 2000, effective filing date.

Zucker has an effective filing date for purposes of 35 U.S.C. § 119 of no earlier than December 29, 2000. Since this date does not precede April 17, 2000, Zucker is not prior art under 35 U.S.C. § 102(e), and, therefore, the rejection based on Zucker must be withdrawn.

Applicants acknowledge the U.S. Patent and Trademark Office's ("PTO") position that removal of Zucker as an available prior art reference removes the basis for withdrawal of the rejection under 35 U.S.C. § 112 (2nd para.) in the October 1, 2003, office action. The basis for the PTO's position is that the skilled artisan would not have been able to assess the level of TRP8 activation and/or inhibition prior to Zucker. Applicants respectfully disagree.

As noted above, the present application and the Provisional Application fully describe the claimed procedures of identifying compounds which have bitter taste. TRP8 activation in taste receptor cells results in an increase in intracellular calcium, which in turn activates calcium dependent downstream messengers leading to transmitter release into the synapse and activation of gustatory nerves (*see* ¶ [0011] of the present application and page 5, lines 6–13 of the Provisional Application. *But see* Hofmann et al., "TRPM5 is a Voltage-modulated and Ca^{2+}-activated Monovalent Selective Cation Channel," *Current Biology*, 13:1153–1158 (2003) (reporting that TRP8 (i.e. TRPM5) is a non-selective monovalent cation channel which, upon activation, results primarily in an influx of sodium) (attached hereto as Exhibit 1). *See also* Liu et al., "Intracellular Ca^{2+} and the Phospholipid PIP_2 Regulate the Taste Transduction Ion Channel TRPM5," *Proc. Natl. Acad. Sci USA*, 100:15160-15165 (2003) (attached hereto as Exhibit 2) and Prawitt et al., "TRPM5 is a Transient Ca^{2+}-activated Cation Channel Responding to Rapid Changes in $[Ca^{2+}]_i$," *Proc. Natl. Acad. Sci. USA*, 100:15166-15171 (2003) (attached hereto as Exhibit 3)). It is possible to monitor TRP8 activation through a number of indirect screening assays by measuring, e.g., changes in intracellular calcium levels and activation of calcium dependent downstream messengers (*see* ¶ [0060] of the present application and page 20, lines 8–10 of the Provisional Application); these screening assays include electrophysiological monitoring and fluorescent dye imaging (*see* ¶ [0059] of the present application and page 19, line 17 to page 20, line 7 of the Provisional Application).

Monitoring ion channel activation through electrophysiological monitoring (e.g., with patch clamp electrodes, intracellular electrodes, and extracellular electrodes) and fluorescent dye imaging of intracellular ions was well known prior to the April 17, 2000, effective filing date. For example, Gillo et al., "Coexpression of Drosophila TRP and TRP-like Proteins in Xenopus Oocytes Reconstitutes Capacitative Ca2+ Entry," *Proc. Nat'l Acad. Sci. U S A.*, 93(24):14146–14151 (1996) (attached hereto as Exhibit 4) discloses electrophysiological and fluorescent dye imaging assays for monitoring a *Drosophila* TRP channel. In particular, the TRP channel was expressed in *Xenopus* oocytes and its currents were monitored with intracellular electrodes. Ca^{2+} entry via the TRP channel was reported to activate an endogenous *Xenopus* calcium-activated chloride channel. TRP channel activity was indirectly monitored by monitoring the change in chloride levels. TRP channel activation was also monitored by measuring Ca^{2+} entry using Ca^{2+}-sensitive fluorescent dyes. Similarly, Burnashev et al., "Fractional Calcium Currents Through Recombinant GluR Channels of the NMDA, AMPA and Kainate Receptor Subtypes," *J. Physiol.*, 485 (Pt 2):403–418 (1995) (attached hereto as Exhibit 5) describes techniques for studying heterologously expressed ion channels in HEK 293 cells using fluorescent dyes and electrophysiological recordings to monitor Ca^{2+}. Hu et al., "Appearance of a Novel Ca^{2+} Influx Pathway in Sf9 Insect Cells Following Expression of the Transient Receptor Potential-like (trpl) Protein of Drosophila," *Biochem. Biophys. Res. Commun.*, 201(2):1050–1056 (1994) (attached hereto as Exhibit 6) discloses monitoring a TRP channel expressed in Sf9 insect cells using the Ca^{2+} indicator dye Fura-2. As demonstrated by this literature, one of ordinary skill in the art, having read the present application would have been fully able to carry out the claimed method as of the April 17, 2000, priority date.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: April 1, 2005

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